Scientific Abstract

In animal models, the partial or complete regression of several types of tumors following administration of recombinant IL-2 protein (Interleukin 2) or adenoviral vectors expressing IL-2 has been reported. VALENTIS, INC. has developed a product of formulated hIL-2 plasmid (IL-2 Gene Medicine) which consists of hIL-2 plasmid formulated with cationic liposomes of DOTMA and the co-lipid cholesterol in a 10% lactose solution.

Data from animal studies supports the idea that IL-2 is effective because it promotes elicitation and expansion of tumor-specific T-cell responses. Requirement of an antigen-specific immune response is supported by findings of a study where recombinant human IL-2 (rIL-2) protein was injected near lymph nodes in patients who had resective surgery one to two weeks later. It was found that rIL-2 induced inflammation, tumor necrosis, and sclerosis, but none of these responses correlated with patient survival. However, there was a direct correlation between survival and the elaboration of $CD25^+$ lymphocytes, $CD25^+$ status indicating expression of the high affinity IL-2 binding component of the IL-2 receptor.

Data from a rodent tumor model demonstrates that intratumoral administration of the IL-2 Gene Medicine results in an increase in the levels of IL-12 (Interleukin 12) and γ-IFN (Interferon gamma) present in tumor and lymph nodes; IL-12 and γ-IFN are known to contribute to generation of $CD25^+$ T-lymphocytes and development of an anti-tumor immune response. When administered intratumorally to tumor-bearing mice, IL-2 Gene Medicine also leads to a decrease in the rate of tumor progression. These data together suggest that administration of the formulated IL-2 plasmid also will lead to the generation of an anti-tumor immune response and subsequent tumor regression, inhibition in tumor progression, improvement in quality of life, and/or prevention of metastasis in humans.

The ability of recombinant IL-2 protein to induce an anti-tumor immune response is documented. However, in order to achieve effective levels of IL-2 at the tumor, high doses of the recombinant protein have been administered systemically. These high doses of recombinant protein have side-effects which include capillary leak syndrome, edema, anemia, fevers and chills, nausea, and hypotension. The proposed research is directed at expressing human IL-2 at a tumor site by cationic liposome-mediated delivery of a therapeutic gene encoding IL-2. This gene therapy will induce local (intra- or peri-tumoral) expression of IL-2 at levels sufficient to induce an anti-tumor response without high systemic concentrations of IL-2. This offers a distinct advantage in that the likelihood of occurrence of side-effects from high doses of IL-2 should be greatly reduced, if not eliminated. In addition, the half-life of IL-2 protein given systemically is only 6-10 minutes, thereby requiring multiple administrations for optimal effect. IL-2 gene therapy is expected to support expression for longer times, obviating the need for multiple administrations. Finally, liposome-mediated DNA delivery does not utilize a recombinant virus for delivery of the therapeutic gene, thereby eliminating potential side-effects associated with virus exposure.

A Phase I trial in patients with head and neck cancer has been completed. This study was designed to evaluate primarily safety and tolerability, and showed that single and multiple intratumoral injections of IL-2 Gene Medicine were safe and well-tolerated. The current study is designed to evaluate the clinical efficacy and safety of IL-2 Gene Medicine in patients with the same condition, and will be compared to treatment with a standard chemotherapy (methotrexate). Each patient will receive multiple (up to 14) intratumoral injection of formulated hIL-2 plasmid over a 12-week period, or methotrexate following standard and approved procedures. Physical examinations and evaluations of clinical chemistry and hematology will be conducted to assess safety and tolerability. In addition, nucleic acid (RNA) studies will be performed with tissue obtained by biopsy to evaluate expression of the IL-2 transgene. Clinical efficacy will be evaluated by clinical and radiological measurements of tumor size, and measurements of survival, time to disease progression, and
'ity of life.